NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

PFIZER INC., PHARMACIA & UPJOHN COMPANY, and PFIZER HEALTH AB, Plaintiffs, v. IVAX PHARMACEUTICALS, INC., Defendant.	**Hon. Dennis M. Cavanaugh** **OPINION** Civil Action No. 07-CV-00174 (DMC)
IVAX PHARMACEUTICALS, INC., and TEVA PHARMACEUTICALS USA, INC., Counterclaim-Plaintiffs, v. PFIZER INC., PHARMACIA & UPJOHN COMPANY, and PFIZER HEALTH AB, Counterclaim-Defendants.	

DENNIS M. CAVANAUGH, U.S.D.J.:

This matter comes before the Court by complaint of Pfizer, Inc. ("Plaintiff" or "Pfizer") against IVAX Pharmaceuticals, Inc. ("IVAX") and Teva Pharmaceuticals USA, Inc. ("Teva") (collectively, "Defendants"). Plaintiff asserts that Defendants infringed claims 4 and 6 of United States Patent No. 5,382,600 (the "'600 patent"). Defendants respond that the '600 patent is invalid as obvious under 35 U.S.C. §103. This Court conducted a non-jury trial on September 17th-23rd,

2009.

This Opinion constitutes the Court's findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a). For the reasons stated herein, a finding in favor of Plaintiff will be entered.

I. BACKGROUND

A. THE '600 PATENT

The '600 patent issued on January 17, 1995, and is entitled "3,3-diphenylpropylamines and pharmaceutical compositions thereof." See Final Pretrial Order - Stipulated Facts ("SF") ¶ 18. There are six inventors named on the '600 patent: Nils Å. Jönsson, Bengt A. Sparf, Lembit Mikiver, Pinchas Moses, Lisbeth Nilvebrant, and Gunilla Glas. SF ¶ 24. At the time the patent application was filed, the inventors worked at Swedish pharmaceutical company Kabi Vitrum AB ("Kabi"), and they assigned their patent rights to Kabi. SF ¶ 25. Pfizer Health AB now holds title to the '600 patent. SF ¶ 26.

The '600 patent claims tolterodine, among other chemical compounds. SF ¶ 40. Tolterodine is the active ingredient in Pfizer's Detrol® and Detrol® LA prescription medications, which are indicated for the treatment of overactive bladder, including the symptoms of urge urinary incontinence, urgency, and frequency. SF ¶¶ 8, 40.

B. THE INFRINGEMENT ACTION

Pfizer holds approved New Drug Application No. 20-771 for tolterodine tartrate tablets, in 1 mg and 2 mg dosage strengths. SF ¶ 6. Pfizer's tolterodine tartrate tablets, which Pfizer sells under the trade name Detrol®, are approved by the United States Food and Drug Administration for the treatment of overactive bladder ("OAB"). SF ¶ 8.

IVAX filed Abbreviated New Drug Application No. 77-006 (the "ANDA") on December 30,

2003, seeking approval to market generic tolterodine tartrate tablets in 1 and 2 mg dosages. SF ¶ 10. On January 10, 2007, IVAX amended its ANDA to include a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV certification") as to the '600 patent, in order to seek FDA approval to market generic tolterodine tartrate tablets before the '600 patent expires. SF ¶ 12.

Pursuant to 35 U.S.C. § 271(e)(2)(A), Pfizer brought this action for infringement of claims 4 and 6 of the '600 patent, both of which cover tolterodine, among other compounds. SF ¶¶ 13, 40. IVAX's parent, Teva, became a party to this suit as a counterclaim plaintiff. SF ¶ 14. Pfizer then asserted an infringement claim against Teva. Id. Defendants IVAX and Teva admited that their generic tolterodine tartrate tablets would infringe claims 4 and 6 of the '600 patent, and asserted affirmative defenses of inequitable conduct and obviousness. SF ¶¶ 14, 17. On December 10, 2008, this Court granted Plaintiff's motion for summary judgment of no inequitable conduct. On April 13, 2009, the Court denied Defendants' motion for reconsideration of that decision.

A bench trial on the issue of obviousness was held from September 17 through September 23, 2009. Defendants seek to render the claims covering tolterodine (claims 4 and 6) invalid by demonstrating that one compound from each claim is obvious–where a patent claim covers multiple compounds, if one compound within the claim is found to be obvious, the entire claim is invalid. See In re Skoll, 523 F.2d 1392, 1397 (C.C.P.A. 1975); see also Ecolochem Inc. v. So. Cal. Edison Co., 1996 U.S. App. LEXIS 13330, at *6 (Fed. Cir. June 5, 1996) ("[I]f . . . one element of the group [of compounds contained in a patent claim] is anticipated or obvious, the patentee is precluded from arguing that the claim is valid.").

The only issue at trial was whether two diphenylpropylamine compounds from the '600 patent, one from claim 4 (the "Claim 4 Compound") and one from claim 6 (the "Claim 6

Compound"), were obvious under 35 U.S.C. § 103. Defendants argued that the Claim 4 and Claim 6 Compounds were obvious in light of two prior art references–a book chapter written by Dr. Paul Janssen, and an article written by Dr. John P. Long.

After the trial, the parties submitted proposed findings of fact and conclusions of law, as well as post-trial briefs.[1]

C. OVERACTIVE BLADDER

Overactive bladder, which includes urge urinary incontinence, is a serious medical condition that affects more than 17 million men and women of all ages, although its incidence increases significantly with age. See Plaintiff's Proposed Findings of Fact ("PPFF") ¶ 51. Urge urinary incontinence results from abnormal contractions of the bladder muscle while the bladder is filling. Id ¶ 50. Prior to the availability of any tolerable pharmaceutical treatment, persons suffering from OAB could either adjust their lifestyle in an effort to manage their symptoms, or resort to using diapers and other paper products. Id ¶ 52.[2] Although the pharmaceutical treatments available prior to the discovery of tolterodine were effective at treating OAB, they "were so severely compromised by attendant side effects . . . that even severe OAB sufferers would forgo their use." Id. ¶ 52.

As explained in the '600 patent, it was known that urinary incontinence was a "cholin-mediated disorder[]" and thus, compounds having anticholinergic properties were useful in treating

[1] Many of the Court's factual findings have been taken from the parties' extensive proposed findings of fact submissions.

[2] Plaintiff introduced the testimony of expert Dr. Rodney Appell, a practicing urologist for nearly 35 years. Dr. Appell served at various times as the Director of the Urodynamics Unit at the Tulane University School of Medicine, and was the F. Brantley Scott Chair in Urology and the Chief of the Division of Voiding Dysfunction and Female Urology at Baylor Medical College. The Court has relied on his testimony regarding the history of pharmaceutical OAB treatments and various alternatives.

the condition. See id. ¶¶ 37, 38. An existing incontinence drug, terodiline, had known side effects. For instance, terodiline "has a very long biological half-life and it is a multi-effect drug also having other pharmacological properties such as Ca-antagonist, noradrenaline antagonist and antihistamine properties as well as a pronounced effect on the heart." Id. ¶ 37. As the '600 patent inventors explained, it was an object of the invention "to provide a novel class of 3,3-diphenylpropylamines having improved anti-cholinergic properties, especially in relation to the effects on these other systems." Id. ¶ 38.

An anticholinergic agent works to treat urinary incontinence by inhibiting or blocking the action of acetylcholine at cholinergic receptor sites, thereby reducing the effects mediated by acetylcholine in the central nervous system (i.e., contraction of the bladder). SF ¶ 41, 42. A number of anticholinergic compounds have been used to treat urge urinary incontinence by preventing abnormal contractions of the bladder. PPFF ¶ 58.

By January 22, 1988, Kabi had marketed two diphenylpropylamines with anticholinergic properties as urinary incontinence treatments: emepronium and terodiline. Id. ¶ 97. Cetiprin, which Kabi had marketed since the mid-1960s for the treatment of urinary incontinence, contained the active ingredient emepronium, a diphenylpropylamine that has anticholinergic activity. Id. ¶ 98. Terodiline, which was approved and marketed for the treatment of urinary incontinence in Europe and Japan between 1986 and 1991, and was to be launched in the United States, has an effect on the heart in addition to the bladder, and was withdrawn from the market in 1992 due to concerns that it might have caused fatal cardiac arrhythmias. Id. ¶ 55. Both drugs had significant side effects. Nonetheless, the active compounds in each were anticholinergic diphenylpropylamines, and had some level of efficacy in treating urinary incontinence.

The inventors of the '600 patent used terodiline as a starting point for further research into a new incontinence medication. Id. ¶ 113. The inventors synthesized a variety of diphenylpropylamines based on terodiline's structure. For example, they modified terodiline by placing different numbers of carbon atoms in the amine group and/or substituents[3] at various positions on the phenyl rings and propyl chain. Id. ¶ 115.[4] The different phenyl ring substituents included halogen atoms like chlorine, bromine, fluorine, as well as carbon-containing groups like methyl, methoxy, nitrocarboxy, and others. Id. ¶ 127. The inventors then conducted tests on the various compounds to observe their pharmacological activities. Based on the results they obtained, the inventors experimented with other potential modifications to the terodiline molecule, the resulting compounds were then synthesized and tested. Id. ¶ 119. This process is referred to as structure-activity relationship testing. For the '600 patent inventors, the process entailed producing hundreds of experimental compounds, which were subjected to a number of diverse biological tests. Id. ¶ 122. As a result of these efforts, the inventors created tolterodine and the other compounds covered by the '600 patent.

D. THE CHALLENGED COMPOUNDS

As noted above, Defendants challenge two compounds within Claims 4 and 6 of the '600 patent as obvious in light of the prior art Janssen Compound. The Janssen Compound and the two

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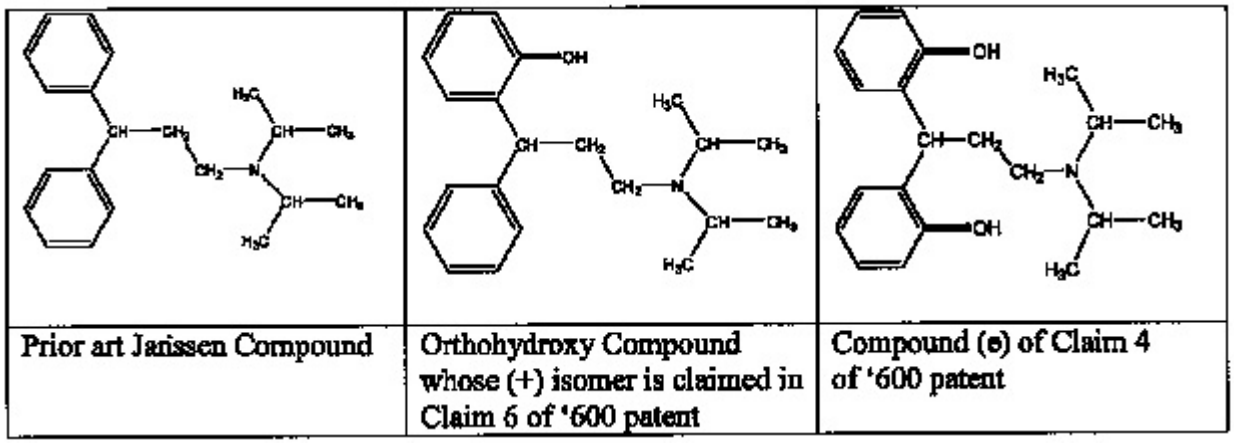
[3] A substituent is an atom or group of atoms placed (or "substituted") at some location on a chemical compound.

[4] Information regarding the work of the inventors was provided by the trial testimony of Dr. Lisbeth Nilvebrant, a fact witness and co-inventor. Dr. Nilvebrant is a pharmacologist who worked at Kabi and Pharmacia & Upjohn in Sweden from 1976 to 2000. See PPFF ¶ 22.

challenged compounds are diphenylpropylamines. A diphenylpropylamine is a molecule comprised of three parts: a diphenyl group (consisting of two phenyl rings); an amine group; and a propyl chain, which connects the diphenyl and amine groups. See Defendants Proposed Findings of Fact ("DPFF") ¶ 62. From this base structure, additional groups may be substituted on the propyl chain and/or each of the phenyl rings. The positions on the phenyl ring are known as the ortho, meta, and para positions. SF ¶ 32. The Janssen Compound and the two claimed compounds are depicted below:



Claim 4 of the '600 patent claims eleven compounds. One of the compounds, the Claim 4 Compound, which Defendants challenge as obvious, is: N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine. The Claim 4 Compound has a hydroxyl group substituted in the ortho position of both of its phenyl rings. The rings are connected to a propyl chain, which links the phenyl rings to a amine nitrogen (which has two isopropyl groups substituted). The Claim 4 Compound, therefore, differs from the prior art Janssen Compound in that it has a hydroxyl group in the ortho position of both phenyl rings.

Claim 6 of the '600 patent is a dependant claim, and it covers the (+)-isomers[5] of the compounds covered by the generic formula in claim 1. The compound in claim 6 that is challenged by Defendants, i.e., the Claim 6 Compound, is: (+)-N,N-diisopropyl-3-(2-hydroxy)-3-phenylpropylamine. The Claim 6 Compound has a hydroxyl group substituted in the ortho position of one of its phenyl rings. Coth phenyl rings are connected to a propyl chain, which links the phenyl rings to an amine nitrogen (which has two isopropyl groups substituted). The Claim 6 Compound is structurally different from the Jannsen Compound in that it has a hydroxyl group substituted at the ortho position of one of its phenyl rings.

II. APPLICABLE LAW

Patents are presumed to be valid. Kao Corp. v. Unilever U.S., Inc., 441 F.3d 963, 968 (Fed. Cir. 2006). A party seeking to invalidate a patent based on obviousness must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007).[6] The Supreme Court has described "clear and convincing" as evidence which

[5] Compounds, such as the Claim 6 Compound, exist in stereoisomers. See DPFF ¶ 152. Compounds with stereoisomers exist in two forms, the (+) and (-) stereoisomers. Id. Each steroeisomer may have different pharmacological activity from the other isomer. Id. ¶ 154. Here, Claim 6 covers the (+) isomer. The Court, as discussed in detail below, finds that the base-structure of the Claim 6 compound was non-obvious. Therefore, the Court need not discuss the obviousness or nonobviousness of the particular isomer claimed in Claim 6.

[6] Defendants argue that their burden of proof in establishing invalidity is by a preponderance of the evidence. They argue that the burden is not the clear and convincing standard because the two prior art references on which they rely were not before the PTO. Although Courts have acknowledged that "a challenger's burden of showing invalidity by clear and convincing evidence may be more easily carried when relying on prior art that was not

produces in the mind of the trier of fact "an abiding conviction that the truth of [the] factual contentions are highly probable." Colorado v. New Mexico, 467 U.S. 310, 316; see also C. MCCORMICK, EVIDENCE § 340, at 796 (2d ed. 1972).

In accordance with "the U.S. Patent Act, an invention cannot be patented if the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." P&G v. Teva Pharms. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009) (internal citation omitted); 35 U.S.C. §103(a). To determine whether a patent is obvious, a Court "must step back in time to before the moment of actual invention, and out of the actual inventor's shoes into those of a hypothetical, ordinary skilled person who has never seen the invention." Eisai Co. v. Teva Pharms. USA, Inc., 2006 U.S. Dist. LEXIS 73516, at *5-6 (S.D.N.Y. Oct. 5, 2006) (citing W.L. Gore & Assocs., Inc. v Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983)). A finding of obviousness, then, "cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." Crown Operations Int'l, Ltd. v. Solutia, Inc., 289 F.3d 1367, 1376 (Fed. Cir. 2002). It is with these principles in mind that courts conduct an obviousness analysis.

Obviousness is a question of law that is based on underlying factual determinations. Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997). The factual determinations that form the basis of the legal conclusion of obviousness include the four "Graham

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considered by the examiner during patent prosecution [and, s]imilarly the challenger's burden may be more difficult to carry when relying on prior art that was considered by the examiner," the clear and convincing evidence standard still must be applied. See Roche Palo Alto LLC v. Ranbaxy Labs. Ltd., 2009 U.S. Dist. LEXIS 90804, *140-41 (D.N.J. Sept. 30, 2009); Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1050 (Fed. Cir. 1988) ("The burden of proof is not reduced when prior art is presented to the court which was not considered by the PTO.").

Factors": **(A)** the level of ordinary skill in the art, **(B)** the scope and content of the prior art, **(C)** the differences between the claimed invention and the prior art, and **(D)** secondary considerations of obviousness, such as commercial success and unexpected results. Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966); see also In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995).

III. DISCUSSION

The Court's findings of fact and conclusions of law with respect to each of the four Graham Factors are presented in turn.

A. PERSON OF ORDINARY SKILL IN THE ART

The first Graham Factor requires the Court to define the level of ordinary skill in the art in 1988, as obviousness is assessed from the perspective of a hypothetical person of skill in the art at the time the patent was filed. See Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1138 (Fed. Cir. 1985). "A person of ordinary skill in the art is . . . presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate . . . [through] expensive, systematic research or by extraordinary insights." Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985); see also Life Techs., Inc. v. Clontech Lab., Inc., 224 F.3d 1320, 1326 (Fed. Cir. 2000).

The parties do not dispute the definition of a hypothetical person of ordinary skill in the art. A person of skill in the art as of January 22, 1988, would be a medicinal chemist or pharmacologist with a master's degree, preferably a doctoral degree, in organic chemistry, pharmacology, or a related field, and would have a basic understanding of drug discovery. See PPFF ¶ 163; DPFF ¶ 34.

B. SCOPE AND CONTENT OF THE PRIOR ART

Under the Second Graham Factor, courts consider the relevant prior art. The prior art consists of references "from the same field or endeavor" or references that are "reasonably pertinent to the particular problem with which the inventor is involved." In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

The two most critical references that form the basis for Defendants' obviousness argument are a book by Janssen and an article by Long. The Janssen reference is a book titled SYNTHETIC ANALGESICS which contains a chapter on diphenylpropylamines ("SYNTHETIC ANALGESICS" or the "Janssen Reference"), which was published in 1960. The Long reference is an article titled "Stereochemical Factors Involved in Cholinolytic Activity" that was published in 1956 ("STEREOCHEMICAL FACTORS" or the "Long Reference"). The parties, and their witnesses at trial, also relied upon BURGER'S MEDICINAL CHEMISTRY, a well-regarded treatise published in 1982 that contains a chapter on anticholinergic compounds.[7]

1. SYNTHETIC ANALGESICS

Dr. Paul Janssen was a pre-eminent chemist of the 20th century. DPFF ¶ 72. Although SYNTHETIC ANALGESICS has "analgesic" in the title, it contains a wealth of information about diphenylpropylamines generally, including their non-analgesic properties. The book describes and discusses hundreds of diphenylpropylamines known in the art and identifies several that had been used as drugs, including the Janssen Compound. Id. ¶ 73.

In a chapter entitled "3,3- Diphenylpropylamines," the book discussed the Janssen

[7] Plaintiff also references GOODMAN AND GILMAN'S PHARMACOLOGICAL BASIS OF THERAPEUTICS, another reputable treatise, as well as the Ph.D thesis of one of the '600 patent inventors, Dr. Nilvebrant.

Compound. The reference explained that the Janssen Compound, "N,N-diisopropyl-3,3-diphenylpropylamine hydrochloride . . . a constituent of Bilagol* Eupharma, is **the most active antispasmodic [i.e., anticholinergic]**[8] and antinicotinic agent of this series (Janssen, 1956, unpublished results)" (emphasis added). Based on this disclosure, Defendants assert that SYNTHETIC ANALGESICS teaches that the Janssen Compound was the most potent anticholinergic diphenylpropylamine known in the prior art. See DPFF ¶ 75.

SYNTHETIC ANALGESICS contains no data regarding the anticholinergic activity or the other properties of the Janssen Compound. See PPFF ¶¶ 170-76. The reference provides no citations to other scientific publications containing data for the Janssen Compound, despite the fact that the reference did in fact provides such citations for many other compounds. See id.

While SYNTHETIC ANALGESICS states that the Janssen Compound is a highly active anticholinergic, it does explain that it is only "half as active as atropine." PPFF ¶ 181. The reference teaches that the Janssen Compound is not the most potent anticholinergic compound, as the compounds in Chapter IV are approximately twice as potent for anticholinergic activity. Id. ¶ 179. The Chapter IV compounds are unlike the Claim 4 and 6 Compounds in that they contain a hydroxyl substitution on the terminal carbon. See id. ¶ 255. These Chapter IV compounds are also different from the claimed compounds (and the Janssen Compound) in that, they are not all bio-available (i.e., they do not absorb well into the systemic circulation, and therefore would not be as useful as a pharmaceutical). See DPFF ¶¶0 89-90.[9]

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[8] Antispasmodic was understood to be synonymous with anticholinergic. DPFF ¶ 94.

[9] On this point the Court credited the testimony of Dr. Gary Glick, Defendants' expert in the fields of organic chemistry and drug development. Dr. Glick is a chaired Professor of chemistry at the University of Michigan. Dr. Glick has extensive experience in organic

Overall, SYNTHETIC ANALGESICS discloses many diphenylpropylamine compounds. Many of these compounds have hydroxyl groups on the terminal carbon, and a number of other diphenylpropylamines have hydroxyl groups attached to alkyl spacers substituted off of the propyl chain. PPFF ¶ 289. These are known as primary and secondary alcohols. Id. Of the thousands of diphenylpropylamines disclosed in SYNTHETIC ANALGESICS, including hundreds having hydroxyl groups, not one has a hydroxyl group–or any other type of group–in any position on a phenyl ring. PPFF ¶ 238.

2. STEREOCHEMICAL FACTORS

The Long Reference is an article titled "Stereochemical Factors Involved in Cholinolytic Activity" that was published in 1956 by Dr. John P. Long. Dr. Long's work, as well as his deposition testimony, was introduced at trial by Defendants.[10]

The teachings of STEREOCHEMICAL FACTORS apply to many types of compounds, including diphenylpropylamines. The portions of the reference that are most critical to the parties' contentions, here, are Dr. Long's observations regarding methods to increase the anticholinergic potency of diphenylpropylamine compounds.

Defendants characterize STEREOCHEMICAL FACTORS as providing a roadmap for a person of ordinary skill in the art to design an improved anticholinergic. In particular, they assert, the reference taught that introduction of a hydroxyl group at certain locations on a compound such as a

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chemistry in both academic and professional settings.

[10] Dr. Long was Defendants' expert in the field of pharmacology. Dr. Long was a professor of pharmacology for over 40 years at the University of Iowa. He has published in excess of 300 articles in peer-reviewed journals, and has extensively studied anticholinergic compounds and their pharmacological effects.

diphenylpropylamine, would increase anticholinergic potency.

Plaintiff contends that the teachings of STEREOCHEMICAL FACTORS are more broad than as described by Defendants. At trial, Plaintiff's expert, Dr. Anton Hopfinger, explained that the reference contains a number of teachings relating to increasing anticholinergic activity in compounds.[11] Although the Court found the testimony of both parties' experts regarding the teachings in the prior art to be informative in certain aspects, as to STEREOCHEMICAL FACTORS the Court largely credited the testimony of Plaintiff's expert, Dr. Anton Hopfinger. Dr. Hopfinger asserted that a hydroxyl substitution should occur **specifically** on the terminal carbon to increase potency.[12] Moreover, in addition to placement of a hydroxyl group at a particular location on a compound (a location different from the one asserted by Defendants), STEREOCHEMICAL FACTORS also teaches that to achieve greater anticholinergic potency, a compound should have: asymmetric cyclic groups; an esther group; and, a quaternary substituted nitrogen. PPFF ¶¶ 263-75.

Plaintiff, in short, argues that Defendants' reading of STEREOCHEMICAL FACTORS is both incorrect, and too narrow. This Court agrees.

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[11] Dr. Hopfinger was Plaintiff's expert in the fields of medicinal chemistry and drug design. Dr. Hopfinger received a PhD in biophysical chemistry from Case Western Reserve University, and did a postdoctoral in biological chemistry at Harvard Medical School. In addition to his academic positions, he has also worked as head of medicinal chemistry at G.D. Searle & Company in the 1980s.

[12] Defendants, in contrast, assert that STEREOCHEMICAL FACTORS teaches that substitution of a hydroxyl group in one of three locations on a diphenylpropylamine will increase anticholinergic potency: in two positions on the phenyl ring (the ortho and meta positions), and on the terminal carbon (i.e., the location where the phenyl ring meets the propyl chain). In fact, they contend that the ortho position of the phenyl ring was the most obvious location for the substitution. The teachings of the Long Reference are discussed in more depth below. See III.C.2, infra.

3. BURGER'S MEDICINAL CHEMISTRY

Although Defendants' obviousness argument was primarily based upon the Janssen and Long References, both parties' experts relied on BURGER'S MEDICINAL CHEMISTRY, a popular treatise. BURGER'S is a prior art reference, published in 1981, that contains a chapter on anticholinergic compounds. The reference identified compounds with a hydroxyl substitution on the terminal carbon (i.e., the carbon where the phenyl rings attached to the propyl chain) as having optimal anticholinergic activity. PPFF ¶ 259. BURGER'S also taught that one way to increase a compound's selectivity was to increase potency. DPFF ¶ 149.[13]

C. DIFFERENCES BETWEEN THE PRIOR ART AND THE CLAIMS AT ISSUE

The Court now turns to the Third Graham Factor. The Federal Circuit has explained that "[w]here, as here, the patent at issue claims a chemical compound, [a court's] analysis of the third Graham factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art." Eisai, 533 F.3d at 1356-57 (Fed. Cir. 2008). To demonstrate that a claimed compound is obvious, a patent challenger must (1) identify a prior art "lead compound," which one skilled in the art would have selected for further research, and then (2) identify some reason in the art to make the "specific molecular modifications" to the lead compound necessary to arrive at the claimed compound. Takeda, 492 F.3d at 1356-57; Altana Pharma AG v. Teva Pharma. USA, Inc., 566 F.3d 999, 1007 (Fed. Cir. 2009) (holding that the party challenging a patent must show that it was obvious for a

[13] As noted below, the Court has determined that Defendants failed to establish a prima facie case of obviousness, and therefore, a full discussion of the parties' arguments regarding the compound's selectivity is unnecessary.

person of ordinary skill in the art to select a certain lead compound, and obvious to make the necessary modifications to the lead compound in order to arrive at the claimed compounds.). If a challenging party fails to make one of these showings by clear and convincing evidence, the patent-in-suit is nonobvious. Takeda, 492 F.3d at 1360.

1. Selection of the Janssen Compound as the Lead Compound

A party challenging a patent must identify a prior art "lead compound" which one skilled in the art would have selected for further research. In other words, Defendants must show by clear and convincing evidence "that the prior art would have led to the selection of [the Janssen Compound]" as a "compound in the prior art that would be most promising to modify in order to improve upon [the compounds anticholinergic properties and] obtain a compound with better activity." Id. at 1357; see Eisai, 533. F.3d at 1358 (noting that patent challengers must show that the asserted lead compound would be the "best candidate . . . for [further] research.").[14]

Defendants assert that the Janssen Compound would be an obvious candidate for a lead compound to select for further research. First, Defendants argue that SYNTHETIC ANALGESICS, as well as other prior art in the field, teach that "diphenylpropylamines [such as the Janssen Compound] make ideal drug candidates and that Dr. Janssen's own work making minor changes in the basic structure of diphenylpropylamines resulted in various drugs, including anticholinergics." Defendants Post-Trial Brief ("DPTB"), at 7. Moreover, they contend, "the Janssen Reference, in a chapter

[14] Defendants argue that the Federal Circuit does not, in all circumstances, require a party to identify a single lead compound. See, e.g., Altana Pharma AG, 566 F.3d at 1008. A patent challenger, then, could demonstrate that a small group of potential lead compounds would be considered likely starting points for further research. Id. Regardless, the Court has determined that the Janssen Compound was not a likely lead compound–or among a group of likely lead compounds–to select for further research.

entitled 3,3-Diphenylpropylamines, singled out the Janssen Compound as the most active antispasmodic [or anticholinergic] in the series of diphenylpropylamines that Janssen considered." Id. at 8. As a highly active anticholinergic, they assert, the compound would be a good starting point for further research because anticholinergics (such as emepronium and terodiline) had previously been used to treat incontinence.

Second, Defendants argue that the Janssen Compound would be a likely lead compound because it was previously used in a marketed pharmaceutical product. DPTB, at 8. Accordingly, a person of skill in the art would have known that the Janssen Compound was safe, it could be manufactured, and it was bio-available. DPFF ¶ 81.

Plaintiff responds that the Janssen Compound would not be an obvious lead compound for further research. First, Plaintiff asserts that the Janssen Compound is not the most potent compound disclosed in SYNTHETIC ANALGESICS. Plaintiff's Post-Trial Brief ("PPTB"), at 14.[15] Second, Plaintiff contends that, while a person of ordinary skill in the art would preferably select a compound used in an existing drug as a lead compound, he or she would have selected a lead from among the

[15] Plaintiff also contends that a person of skill in the art would not even consider SYNTHETIC ANALGESICS because the title of the book was SYNTHETIC ANALGESICS. Plaintiff argues that the title–referring to analgesics instead of anticholinergics–would cause a person of skill in the art to omit the reference when considering the prior art on anticholinergic compounds. The Court disagrees. The book was written by a preeminent scholar in the relevant field, and contained an entire chapter dedicated to diphenylpropylamines. The title of the chapter that Defendants rely on for their obviousness argument is titled 3,3-Diphenylpropylamines–the claimed subject matter of the '600 patent. Plaintiff argues that if a person of ordinary skill in the art was researching improved incontinence treatments, "they wouldn't go to a book on analgesics." However, the introduction to SYNTHETIC ANALGESICS explains that diphenylpropylamines also have non-analgesic (i.e., antispasmodic/anticholinergic) properties. Finally, as both parties agree, diphenylpropylamines were known in the art, as of 1988, to have anticholinergic effects. In light of these factors, the Court agrees with Defendants that a person of ordinary skill in the art would likely consider SYNTHETIC ANALGESICS in surveying the prior art prior to the development of a new compound to treat incontinence.

known urinary incontinence treatments. Id. at 19. Third, the Janssen Compound was known to have side effects that would discourage researchers from using the compound as a lead to begin designing a new drug. Id. at 18. Fourth, Plaintiff asserts that a person of ordinary skill in the art would not have chosen the Janssen Compound because there was no data for the compound in SYNTHETIC ANALGESICS (or any other publication referenced therein). Id. at 16.

The Court recognizes that a wide range of factors must be considered to determine whether a particular compound would be a likely lead compound for further research in drug development. See, e.g., Takeda, 492 F.3d at 1358 (finding that one of ordinary skill in the art would not have chosen the proposed lead compound because "there were many promising, broad avenues for further research" and the asserted lead compound had a number of"adverse side effects"); Daiichi Sankyo Co. v. Mylan Pharms., 2009 U.S. Dist. LEXIS 67978, at *37-38 (D.N.J. July 30, 2009) (observing that "a medicinal chemist of ordinary skill [seeking a potential lead compound] considers a multitude of factors, including the lead compound's potency . . . [and the availability of] robust packages of real data, such as binding activity, intravenous activity, oral activity, specificity . . .). To determine whether it would be likely for a particular compound to be selected as a lead for further research, then, no one characteristic of the compound is necessarily dispositive. With these principles in mind, the Court will consider the parties' various arguments regarding the likelihood of the Janssen Compound being selected as a lead compound for further research in developing an improved incontinence treatment.

(a) *Was the Janssen Compound the Most Active Anticholinergic Compound Available in the Prior Art?*

As to whether a person of skill in the art would consider the Janssen Compound the most

active anticholinergic agent available, the Court does not agree with either parties' argument in its entirely.

The Court agrees with Defendants that anticholinergic potency would be an important consideration for a person of skill in the art searching for a lead compound. See DPFF ¶ 78. The Court also agrees with Defendants that of the compounds discussed in SYNTHETIC ANALGESICS, the Janssen Compound appears to be among the most potent anticholinergics that would be useful in designing an incontinence drug.[16]

The Court, however, agrees with Plaintiff on a more critical point–even if the Janssen Compound was among the most potent/bioavailable anticholinergics in SYNTHETIC ANALGESICS, the prior art as a whole does not indicate that the Jansen Compound would be the most potent anticholinergic available.

SYNTHETIC ANALGESICS cannot be read in isolation. "[T]he correct test of invention or nonobviousness focuses on the teachings of the prior art as a whole, not the disclosures of individual references taken singly." 2-5 CHISUM ON PATENTS § 5.04, n.14; Novartis Pharms. Corp. v. Teva Pharms. USA, Inc., 2007 U.S. Dist. LEXIS 65792, at *16-17 (D.N.J. Sept. 6, 2007) (finding that even if one reference points to a particular lead compound, this suggestion is negated when other prior art references contain conflicting teachings); Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc., 456 F. Supp. 2d 644, 656 (D.N.J. 2006) (noting that the prior art contained "more likely starting points for the development of an improved atypical antipsychotic drug"). Accordingly, the Court must determine whether SYNTHETIC ANALGESICS would teach a person of skill in the art that the

[16] Some of the disclosed compounds, despite their high potency, would not have been likely selections as lead compounds in light of their low bioavailability. DPFF ¶¶ 89, 90.

Janssen Compound was a likely lead compound when read in light of other prior art (including STEREOCHEMICAL FACTORS, the second reference on which Defendants' obviousness argument relies).

The Court finds that the teachings of STEREOCHEMICAL FACTORS would cast doubt upon selection of the Janssen Compound as a likely lead. STEREOCHEMICAL FACTORS teaches that to achieve highest anticholinergic potency, a compound should have: asymmetric cyclic groups; a hydroxyl substituted on the compound's terminal carbon; a quaternary substituted nitrogen; and an esther group. PPFF ¶¶ 263-75. The Janssen Compound, however, has none of these four characteristics.[17] Accordingly, the Janssen Compound was a less likely lead compound choice than compounds that shared one or more of the four traits that STEREOCHEMICAL FACTORS describes as useful to achieve increased anticholinergic potency. See PPFF ¶ 182.

To determine whether a person of skill in the art would have considered the Janssen Compound to be the most potent anticholinergic compound available, the Court has considered the teachings of both SYNTHETIC ANALGESICS and STEREOCHEMICAL FACTORS. Both references would have been known to a person of ordinary skill in the art, and therefore, they must be viewed together in ascertaining the relevant teachings of the prior art in 1988. See Akzo N.V. v. U.S. Int'l Trade Comm'n, 808 F.2d 1471, 1481 (Fed. Cir. 1986) ("Defendants cannot pick and choose among individual parts of assorted prior art references as a mosaic to recreate a facsimile of the claimed

[17] As discussed further below, Defendants argue that STEREOCHEMICAL FACTORS teaches that the hydroxyl substitution must be made in one of three locations (including the phenyl ring). See Section III.C.2. The Court disagrees with this characterization of the reference's teachings. Nonetheless, even if that was the teaching of STEREOCHEMICAL FACTORS, the Janssen Compound would still only have one of the several attributes that the reference suggests are desirable for optimal anticholingeric activity.

invention.") (internal quotations omitted); Novartis Pharms. Corp., 2007 U.S. Dist. LEXIS 65792, at *16-17.

The propr art references, in light of the expert testimony at trial, illustrate that a person of ordinary skill in the art would not have believed the Janssen Compound to be the most potent anticholinergic available.

(b) *Did Use of the Janssen Compound in an Existing Medication Make it a Likely Lead Compound?*

Under the circumstances here, the Janssen Compound's use in an existing pharmaceutical product does not support a finding that it would be a likely lead compound.

Defendants assert that the Janssen Compound's use in the drug Bilagol indicates that it is relatively safe and bioavailable. See DPFF ¶ 81. Typically this fact would make the compound a more likely candidate for lead compound. Here, however, as of 1988 there were a number of potential compounds being used in existing drugs that were **specifically designed to treat urinary incontinence**. PPFF ¶ 196. These other compounds, then, were similarly safe and bioavailable, and were being used to treat the particular condition the inventors were addressing. Id. The most notable example of such a compound is terodiline, which was in fact the inventors' lead compound for further research. PPFF ¶ 114. In addition to terodiline, the inventors used five other compounds as leads for further research–all of which were used to treat urinary incontinence. PPFF ¶ 196. Although research for drug development would likely have begun with compounds utilized in pharmaceutical products, here, a person of ordinary skill in the art would have begun their research with compounds that were currently being used in urinary incontinence drugs–as such drugs had already achieved a level of success as of 1988.

The fact that the Janssen Compound was the active ingredient in a marketed drug does not make it a likely lead compound for further research where, as here, a number of other potential lead compounds were already being used specifically to treat urinary incontinence.

(c) *Do the Side Effects Associated with the Janssen Compound Prevent it from Being Selected as a Lead Compound?*

The Janssen Compound's known side effects do not substantially weigh against its selection as a lead compound under the facts of this case.

Plaintiff urges that the side effects associated with the Jannsen Compound would prevent it from being selected as a lead compound. As explained in SYNTHETIC ANALGESICS, the Janssen Compound was the "most active antispasmodic [i.e., anticholinergic] **and nicotinic** agent" in the series of compounds discussed in Chapter 3 of the reference. PPFF ¶ 171. Plaintiff argues that a person of ordinary skill in the art seeking to make an incontinence drug would not choose a compound having both antimuscarinic and antinicotinic properties, because antinicotinic activity could cause severe, unintended side effects. PPFF ¶ 192. For instance, antinicotinics can paralyze skeletal muscle, disrupt the autonomic nervous system, and affect an individual's heart rate, pupils, salivation, urination, and digestion. PPFF ¶¶ 190, 191. Plaintiff argues that the likeliness of the Janssen Compound being selected as a lead is dramatically reduced as a result of these known side effects. See Takeda, 492 F.3d at 1359 (negative side effects could dissuade one of skill from using a particular compound as a starting point). While Plaintiff accurately states the law, this argument is not compelling here, as the actual lead compound(s) chosen by the inventors caused significant side effects as well. See DPFF ¶ 97.[18] Accordingly, the known side effects cannot be considered a

[18] The inventors began their research with drugs that had known side effects, and then modified the compounds so as to minimize these properties in relation to the desirable properties.

significant deterrent in selecting the Janssen Compound as a lead.

Although the known defects of the Janssen Compound do make it a slightly less desirable compound for further research, in light of the side effects associated with many of the potential lead compounds, this factor only minimally weighs against its selection as a lead.

(d) *Would the Lack of Existing Data Regarding the Janssen Compound Dissuade a Person of Skill in the Art from Selecting it as the Lead Compound?*

Plaintiff asserts that there was no published data available for the Janssen Compound compared to other compounds, and that this would prevent the compound from being selected as a lead for further research. See PPTB, at 17.

Although this Court does not agree with Plaintiff's contention that a compound with little or no published data available would **never** be selected as a lead compound, it is sensible to conclude that a person of ordinary skill in the art would prefer to begin drug development research with a compound that has available data. See PPFF ¶¶ 176-78; Daiichi Sankyo, 2009 U.S. Dist. LEXIS 67978, at *38 ("When selecting a lead point for development, a medicinal chemist of ordinary skill considers a multitude of factors . . . [including whether a potential compounds has] robust packages of real data" available.). The Court credits Dr. Hopfinger's trial testimony on this point, and notes that other courts have made similar findings. See, e.g., Daiichi Sankyo, at *38. This fact that there was no published data for the Janssen Compound, however, only slightly weighs against selection of the compound as a lead.

Here, SYNTHETIC ANALGESICS does not contain published results (or citations to published

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DPFF ¶ 97. Under the facts of this case, the presence of negative side effects does not strongly weigh against selection of the Janssen Compound as a lead. The Court's conclusion on this point would be different if it were found that the actual lead compounds (e.g., terodiline) did not also cause undesirable side effects.

results) relating to the Janssen Compound's properties. Dr. Janssen's status in the field of medicinal chemistry, however, would permit a person of skill in the art to rely on his conclusions regarding the various properties of the compounds he discusses in his article. See DPFF ¶ 87.[19] The Court recognizes that the lack of published data is not preferable. Moreover, the reference provides citations to scientific publications for many of the other compounds discussed therein, and does not do so for the Janssen Compound. PPFF ¶ 175. These facts might typically make the compound a less likely candidate for further research. Despite these deficiencies, the Court finds that a person of ordinary skill in the art would find credible the observations of a preeminent scholar in the field.

The lack of data regarding the Janssen Compound would only minimally weigh against its selection as a lead compound for further research.

* * * * *

The Court has considered the evidence of record and the parties' legal arguments with respect to the likelihood of the Janssen Compound being a potential lead compound for further research. Viewing the prior art as a whole, this Court finds that a person of ordinary skill in the art would not have selected the Janssen Compound as a lead compound. The Court's determination is supported by the testimony of Dr. Hopfinger, as well as that of Dr. Long (the author of STEREOCHEMICAL FACTORS, a key reference relied upon by Defendants).[20] Defendants have failed to show by clear and

[19] The Court finds the testimony of Dr. Glick regarding Dr. Janssen's status in the field to be compelling. This opinion was not contradicted, and indeed was confirmed, by Plaintiff's witness Dr. Hopfinger. See DPFF ¶ 87.

[20] Dr. Long, through his deposition testimony, did not unambiguously indicate that the Janssen Compound (or even diphenylpropylamines more generally) would be the most likely place to begin further research. PPFF ¶¶ 207-09. All he did was speculate as to whether a compound (or type of compound) would be a likely candidate for further research. See e.g., id. The Court finds that Dr. Long's credible testimony was critical for what it did not say. His

convincing evidence that the Janssen Compound was a likely lead compound, and therefore, have failed to establish a prima facie case of obviousness.

2. **Reason in the Prior Art that Would Cause a Person of Ordinary Skill in the Art to Make the Specific Molecular Modifications to the Lead Compound to Arrive at the Claimed Compounds**

As discussed above, Defendants have not demonstrated that the Janssen Compound was a likely lead compound for further research, and cannot establish a prima facie case of obviousness. Moreover, even if the Janssen Compound was a likely lead compound, Defendants have failed to "identify some reason that would have led a chemist to modify [the Janssen] compound in a particular manner" to arrive at the challenged compounds (i.e., the Claim 4 and Claim 6 Compounds). Takeda, 492 F.3d at 1356-57. For a second reason, then, Defendants have not established a prima facie case of obviousness. See id.

Defendants contend that the Long Reference, an article titled STEREOCHEMICAL FACTORS, taught a person of ordinary skill in the art to make "the specific molecular modifications necessary [to the Janssen Compound]" to arrive at the two challenged compounds in claims 4 and 6 of the '600 patent. See id. at 1356-57 (quoting In re Deuel, 51 F.2d 1552, 1558 (Fed. Cir. 1995)). More specifically, Defendants assert that STEREOCHEMICAL FACTORS taught that the introduction (i.e., substitution) of a hydroxyl group onto a diphenylpropylamine compound at a distance of approximately 5-7 Å from the amine would lead to a significant increase in anticholinergic

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equivocal statements as to a likely lead compound strongly support this Court's finding that Defendants have not established, by clear and convincing evidence, that the Janssen Compound would have been selected for further research by a person of skill in the art.

activity.[21] Applying these teachings to the Janssen Compound, they argue that a person of skill in the art would begin with the Janssen Compound, and place a hydroxyl group on some location on the compound within a distance of 5-7 Å of the nitrogen. By so doing, Defendants argue, a person of ordinary skill in the art would expect to achieve greater anticholinergic activity. Defendants conclude that it was obvious to apply the teachings of STEREOCHEMICAL FACTORS to the Janssen Compound, to create the Claim 4 and Claim 6 Compounds–both compounds have the Janssen Compound's structure with a hydroxyl group placed on the ortho position of the phenyl ring(s), i.e., within the 5-7 Å distance.[22]

Plaintiff asserts that STEREOCHEMICAL FACTORS did not teach that the placement of a hydroxyl within 5-7 Å from the amine of a diphenylpropylamine achieves the greatest level of anticholinergic activity.[23] Plaintiff, instead, asserts that the reference more specifically teaches that the hydroxyl substitution should occur at the terminal carbon (and not at one of the phenyl ring positions). Plaintiff bases its argument on three observations. First, "[e]very compound in Long with

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[21] Å stands for angstrom. An angstrom is a unit of molecular measurement used by chemists equal to 1 x 10^{-9} meters.

[22] The Claim 4 Compound has a hydroxyl at the ortho position of each of its two phenyl rings. The Claim 6 Compound has a hydroxyl group at the ortho position of one of its phenyl rings. The Court finds that the hydroxyl groups in each compound are within the 5 to 7 Å distance of the nitrogen. Defendants' witnesses Dr. Glick and Dr. Long (the author of STEREOCHEMICAL FACTORS) both testified that they believed the ortho position of a phenyl ring to be among the various positions of a diphenylpropylamine, such as the Janssen Compound, that are with 5 to 7 Å of the nitrogen. See DPFF ¶¶ 125, 126. The Court found this testimony to be credible.

[23] Plaintiff alternatively asserts that, even if STEREOCHEMICAL FACTORS did generally teach placement of a hydroxyl within 5 to 7 Å of the amine increases anticholinergic potency, the ortho position is not 5 to 7 Å from the amine on the Janssen Compound. The Court disagrees with this assessment. See, note 22 supra.

a hydroxyl group–diphenylpropylamine or otherwise–has the hydroxyl **on the terminal carbon, not on the phenyl ring** or in any other position." See PPFF ¶ 247. Accordingly, Plaintiff asserts, the Long Reference teaches that a hydroxyl substitution is appropriately made at the terminal carbon, not the phenyl ring. Second, STEREOCHEMICAL FACTORS indicates that a hydroxyl group provides increased activity when placed "**next to** an inductive (or polarizable) group such as a phenyl ring." See PPFF ¶ 249 (emphasis in original). The reference, therefore, teaches that the hydroxyl substitution is not to be made on the phenyl ring, but rather at a location on the compound adjacent to the phenyl ring (i.e., the terminal carbon). See id. Third, Plaintiff asserts that BURGER'S MEDICINAL CHEMISTRY, a well-regarded prior art treatise relied on by both parties, indicates that placing a hydroxyl on the terminal carbon is the optimal substitution for increasing anticholinergic properties. PPFF ¶ 259-260. In light of these considerations, Plaintiff argues that the prior art as a whole "teaches away" from placing the hydroxyl on the ortho position of the phenyl ring(s). As such, it would not have been obvious to modify the Janssen Compound to create the Claim 4 and Claim 6 Compounds.

The Court agrees with Plaintiff, and finds that the prior art teaches away from placing the hydroxyl on the ortho position of the phenyl ring(s). A reference "teaches away" from a particular invention when it leads one skilled in the art "in a direction divergent from the path that was taken by the [inventors]." Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 885 (Fed. Cir. 1998) (quoting In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994)). "[R]eferences that teach away cannot serve to create a prima facie case of obviousness." McGinley v. Franklin Sports, Inc., 262

F.3d 1339, 1354 (Fed. Cir. 2001).[24]

STEREOCHEMICAL FACTORS contains a single observation that introduction of a hydroxyl group approximately 5-7 Å from the nitrogen (i.e., the amine) will lead to a significant increase in anticholinergic activity. There are several locations on a diphenylpropylamine that are within this distance, including the ortho position of the phenyl rings. See DPFF ¶¶ 125, 126. This fact notwithstanding, STEREOCHEMICAL FACTORS has a number of additional teachings indicating that one particular location within the 5-7 Å distance is the ideal location to substitute a hydroxyl for increased anticholingeric activity. Specfically, the reference teaches that to achieve highest anticholinergic potency, a compound should have a hydroxyl group **next to** the phenyl ring–i.e., on the terminal carbon of the propyl chain.[25]

The Court's finding that STEREOCHEMICAL FACTORS taught placement of a hydroxyl group on the terminal carbon is confirmed by two additional prior art references, which the Court must consider to understand the teachings of Long's article from the point of view of a person of ordinary skill in the art. See In re Gorman, 933 F.2d at 986 (quoted in 2-5 CHISUM ON PATENTS § 5.04) (recognizing that Courts must consider the prior art as a whole in determining obviousness); Akzo N.V. v. U.S. Int'l Trade Comm'n, 808 F.2d at 1481 (same). First, SYNTHETIC ANALGESICS, published four years after STEREOCHEMICAL FACTORS, discloses many diphenylpropylamines. Of the thousands of diphenylpropylamines disclosed in the reference, including hundreds having

[24] Defendants argue that the reference does not reach the level of "teaching away" from the claimed invention. See DPTB, at 20. The Court disagrees with their asserted definition of teaching away. Even if this were the case, the Court still finds the reference's teachings to be substantially different from the interpretations suggested by Defendants.

[25] As noted above, the reference did not disclose a single hydroxyl substitution on the phenyl ring of a compound.

hydroxyl groups, not one has any substituent–let alone a hydroxyl–in any position on a phenyl ring. PPFF ¶ 238. Second, BURGER'S MEDICINAL CHEMISTRY, published twenty years after STEREOCHEMICAL FACTORS, contains a chapter on anticholinergic compounds. BURGER's teaches that compounds with a hydroxyl group on the "third carbon from a nitrogen atom" (i.e., the terminal carbon of a diphenylpropylamine)–have "optimal anticholinergic activity." PPFF ¶ 259. These two references confirm the Court's finding that STEREOCHEMICAL FACTORS taught that placement of a hydroxyl on the terminal carbon of the Janssen Compound would be the best way to achieving increase anticholinergic activity. The Court finds that the prior art did not disclose (to a person of skill in the art) a reason to substitute a hydroxyl at the ortho position of the Janssen Compound to achieve a new, more potent anticholinergic compound.

Moreover, in addition to the prior art teachings regarding the location for hydroxyl substitution, the Court also finds that STEREOCHEMICAL FACTORS taught away from the modifications to the Janssen Compound for another reason. The reference teaches that anticholingeric activity is optimized when, in addition to the hydroxyl substitution, a compound has three characteristics: asymmetric cyclic groups, an esther group, and a quaternary substituted nitrogen. These characteristics are not shared by the Claim 4 and 6 Compounds. Therefore, because only one of the four STEREOCHEMICAL FACTORS teachings can even arguably be applied to the Janssen Compound, a person of skill in the art would most likely not rely on the reference's teachings in modifying the Janssen Compound for increased anticholinergic potency. See Gurley, 27 F.3d at 552 ("A reference is said to teach away when a person of ordinary skill in the art . . . would be discouraged from the path set out in the prior art").

As explained above, the prior art does not provide a person of skill in the art a reason to make

the requisite substitutions to the Janssen Compound to create the claimed compounds. See Takeda, 492 F.3d at 1357 (construing KSR, 550 U.S. at 425-26) ("[I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."). Instead, it appears that Defendants selectively combined two isolated teachings of prior art–to the exclusion of other relevant teachings–to recreate the claimed compounds. However, "mere identification in the prior art of each component of a composition does not show that the combination as a whole lacks the necessary attributes for patentability, i.e. is obvious." Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1379 (Fed. Cir. 2006); see also Processing Corp. v. Am. Maize-Products Co., 840 F.2d 902, 907 (Fed. Cir. 1988) (noting that in considering obviousness, "[c]are must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.") (internal citations omitted). Defendants' assertion that the prior art made it obvious to modify the Janssen Compound in light of STEREOCHEMICAL FACTORS to achieve the claimed compounds can only be the product of impermissible hindsight. See KSR, 550 U.S. 398, 421 (cautioning against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness); Eli Lilly, 471 F.3d at 1379.

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To summarize, Defendants argue that one of STEREOCHEMICAL FACTORS' many teachings indicates that a hydroxyl substitution on one of several locations (among which is the ortho position of phenyl ring) would be a factor in increasing anticholinergic potency. The Court finds this to be

an improper reading of the prior art for two reasons. First, STEREOCHEMICAL FACTORS (and the other prior art references) more specifically taught that the hydroxyl placement should occur at the terminal carbon location for optimal potency. Second, regardless of the precise location of hydroxyl placement, Defendants' argument implies, without justification, that a person of skill in the art would apply STEREOCHEMICAL FACTORS' hydroxyl substitution teaching to the Janssen Compound while ignoring the reference's other teachings.[26]

Defendants have not established "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention." P&G, 566 F.3d at 994 (quoting Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007)). The Court finds that STEREOCHEMICAL FACTORS and the additional prior art available in 1988, did not provide a person of ordinary skill in the art a reason to modify the Janssen Compound to arrive at the claimed compounds of claims 4 and 6 of the '600 patent.

D. OBJECTIVE INDICIA OF NONOBVIOUSNESS

If a patent challenger establishes a prima facie case of obviousness under the first three Graham Factors, the patent holder can rebut the prima facie showing (pursuant to the fourth Graham Factor) by providing objective evidence of nonobviousness. Here, however, as Defendants have failed to establish a prima facie case, the Court need not consider the objective indicia of nonobviousness. See Takeda, 492 F.3d at 1363 ("In light of our conclusion that [the patent

[26] In other words, even assuming that STEREOCHEMICAL FACTORS taught that the phenyl ring was a viable location for hydroxyl substitution to increase anticholinergic potency, there is no reason that a person of skill in the art would apply this one teaching, while not applying the reference's teachings that anticholingeric activity is optimized when a compound has asymmetric cyclic groups, an esther group, and a quaternary substituted nitrogen.

challenger] failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness.); Unigene Labs., Inc. v. Apotex, Inc., 2009 U.S. Dist. LEXIS 78051, at *48-49 (S.D.N.Y. Aug. 31, 2009) (same).

IV. CONCLUSION

For the reasons set forth above, Defendants have failed to demonstrate that the '600 patent is obvious by clear and convincing evidence. Counsel are directed to submit an order of judgment consistent with this Opinion.

S/ Dennis M. Cavanaugh
Dennis M. Cavanaugh, U.S.D.J.

Date: January 20, 2010
Orig.: Clerk
cc: All Counsel of Record
Hon. Mark Falk, U.S.M.J.
File